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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,185	12/29/2000	Nicholas Hunt	P66036US1	5831

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EXAMINER

LI, BAO Q

ART UNIT

PAPER NUMBER

1648

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/750,185	HUNT, NICHOLAS
	Examiner Bao Qun Li	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 31 October 2002.

2a) This action is **FINAL**.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 119-250 is/are pending in the application.

4a) Of the above claim(s) 119-250 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 213-231 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input checked="" type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>6</u>	6) <input type="checkbox"/> Other: _____

## **DETAILED ACTION**

Preliminary amendment has been acknowledged. Claims 1-118 have been canceled.

Abstract has been amended. New claims 119-250 have been added. Claims 119-250 are pending.

### ***Sequence requirements***

This application contains sequence disclosures on pages 75 and 76 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with both these requirements in the time period set forth in this office action will be held non-responsive.

### ***Election/Restrictions***

1. Applicant's election without traverse of Group XVIII, claims 213-231 in the scope of the virus like particle is made from retrovirus (2a)'s capsid protein (1a) fused with a receptor (a) through an electrostatic forces encoded by using two signal sequences (2) and VLP is released through a membrane budding mechanism (a) in Paper No. 9 is acknowledged. Claims 213-231 to the scope of a retrovirus (2a)'s capsid protein (1a) fused with a receptor (a) through an electrostatic forces (2) encoded by using two signal sequences and VLP is released through a membrane budding mechanism (a) are considered before examiner.
2. Applicant is requested to amend the claims 213-231 to the scope of a retrovirus (2a)'s capsid protein (1a) fused with a receptor (a) through an electrostatic forces (2) encoded by using two signal sequences and VLP is released through a membrane budding mechanism (a) for reflecting the examination on the merits.
3. Applicant is also reminded to cancel the claims 119-212 and 232-250.

### ***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 213-321 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 213 is very confusing in that the metes and bounds of first amino acid sequence and the second amino acid sequence of first component are not defined; the metes and bounds of target molecule complex of the first component and the target molecule of the second component are not defined; and the first amino acid sequence and the second amino acid sequence of signal molecule and not defined. The claim is interpreted in light of the specification, however, the specification does not teach the definitions of the first amino acid sequence and the second amino acid sequence of first component; the target molecule complexes of the first component and the second component respectively; and the first amino acid sequence and the second amino acid sequence of signal molecule. The claim is also very unclear in that what the relationship between each elements or sequences that constitute the virus like particle. For example, what the structural relationship between the two target molecules of the first component and the second component, what the structural relationship with the signal sequences with each of the target molecules. If Applicant wishes to claim a particular sequence(s) such as peptides of K-coil and E-coil that are able to link two or more peptides or polypeptides to be dimerized or form  $\alpha$ -helical coiled-coil structure, please amend the claim to a particular sequence(s) that is intended in the claim. This affects the dependent claims 214-231.

7. Claim, 218, 226, 227 and 230 are vague and indefinite in that the metes and bounds of "a fragment" are not defined. Although the claim is interpreted in light of the specification; however, the specification does not teach what the definitions of "a fragment" are.

8. Furthermore, claim 218 is also vague in that the use of a relative term of "derivatives". Since the specification does not provide a standard for ascertaining the requisite degree of derivation and the term of "derivation" has many interpretations, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore the claim is considered as indefinite.

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9. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to incorporate or encapsulate a proteinaceous target molecule complex into a virus like particle or physically associate a proteinaceous target molecule complex with a virus like particle, in particular, in which manner that each first amino acid sequence is linked with a second amino acid sequence, in which non-covalent manner that first amino acid sequence is linked or incorporated with target molecule, how the target molecule is constructed into homo-dimer, hetero-dimers, or homo-oligomers or hetero-oligomers.

10. Claim 225 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to measure the binding constant  $K_{ass}$  between the said signal molecule and the target molecule.

***Claim Rejections - 35 USC § 112***

11. Claim 213-231 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using an insect cell system to produce a viral like particle comprising a retroviral gag gene as a signal molecule and a G-protein-coupled receptor, such as EGFR as a target molecule, wherein the two proteins are associated through an electrostatic force produced by fusing the Gag protein to the K-coil and EGF receptor to E-coil to form a coiled-coil heterodimer structure, does not reasonably provide enablement for using any or all signal amino acid sequence linked to any or all sequence, which is able to non-covalently associate with other amino acid sequence that is linked to any or all target sequence to produce a virus like particle. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

12. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Thektronics Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighing many factors. These factors were outlined in Ex parte

Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

1) & 2) State of the art and unpredictability of the field.

Although the method for making viral like particle comprising a receptor, such as CD4, by using chimeric retroviral gag and/or env protein are known in the art (Schubert et al. J. Virol. 1992, Vol. 66, pp. 1579-1589). However, the method for using any or all two amino acid sequences or fragment thereof to make a viral like particle is unpredictable.

3) Number of working examples.

Applicants only present examples of a method for making viral like particle, which comprises a retroviral gag gene (signal molecule) and a receptor (target molecule) in a baculovirus expression system by co-transfected the cells with a construct comprising a signal molecule of retroviral gag gene sequence tagged with a peptide  $_{\text{NH}_2}\text{-K-V-S-A-L-K-E-COOH}$  K-coil at its C-terminal and another construct comprising a target molecule, such as EGFR tagged with another peptide molecule  $_{\text{NH}_2}\text{-E-V-S-A-L-E-K-COOH}$  E-coil at its C-terminus in a insect cell expression system, wherein the two proteins are associated through a coiled-coil structure mediated by an electrostatic force.

However, the specification presents no working examples of making any or all viral like particle with any or all two sequences or fragment thereof of a receptor or mutant of a capsid protein through any or all non-covalent manner as cited in claims 213.

4) Amount of guidance presented in the specification.

Applicants present no guidance on how to make the fragment of a receptor or mutant of a capsid protein and non-covalently linked each other by any or all signal sequences to make a viral like particle.

5) Scope of the claims.

The claims are broadly read to uses any or all two amino acid sequences to make a viral like particle through any or all non-covalent manner.

6) & 7) Lever of the skill in the art and nature of the invention.

The level of the skill in this art is high, which require high technology to design, construct and produce a virus like particle.

Given the above analysis of the factors, which the courts have determined are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to conducted undue and excessive experimentation in order to practice the claimed invention.

Hence, considering large quantity of experimentation needed, the unpredictability of the field, the state of the art, and breadth of the claims, it is concluded that undue experimentation would be required to enable the intended claim.

### ***Claim Rejections - 35 USC § 102***

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 213, 215-223, 226-229 and 231 are rejected under 35 U.S.C. 102(b) as being anticipated by Schubert et al. (J. Virol. 1992, Vol. 66, pp. 1579-1589).

14. Schubert et al. teach a method for generating a viral like particle comprising a HIV CCD4 receptor and HIV envelope protein by inserting the gene encoding the receptor CD4 into the genome encoding the glycoprotein of the vesicular stomatitis virus (CD4/G) and it serves as a target molecule for targeting the cells expressing the CD4 molecule on the cell surface. Co-infecting the Hela cells two populations of vaccinia viruses, one express CD4/G and other HIV-1 envelope. In this system, the HIV envelope protein serves as a signal molecule and the CD4 receptor serves as the target molecule, which is also heterologous to the viral like particle genome. The viral like particle expresses both CD4 receptor molecule and Envelope protein on the surface of the virus like particles (See entire document). The virus like particle is assembled through the cellular membrane budding process. Therefore, the claimed invention is anticipated by the cited reference.

15. Claims 213, 215-223, 226-229 and 231 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Es et al. (EP 0960,942A2).

16. Van Es disclose a method for making a retroviral like particle by incorporating the host cell with hCAT1 binding peptide into the envelope protein of the MoMLV as a target molecule and make a viral like particle for delivering a therapeutic gene. The MuLV is a retrovirus, the

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process of the assembly the viral like particle would be inherently through the budding of the cell membrane system. Therefore, the claimed invention is anticipated by the cited reference.

17. Claims 213, 215-217, 219, 226,-228, and 231 are rejected under 35 U.S.C. 102(b) as being anticipated by Kingsman et al. (WO 88/03563A1).

18. Kingsman et al. teach a method for making a viral like particle comprising first amino acid sequence and a second amino acid sequence, wherein the first amino acid sequence is derived from an RNA retrovirus and confers on the fusion protein the ability to assemble into a viral like particles. The second amino acid sequence encodes the biological active molecule, such as antigen as a target molecule to be used as a therapeutic agent (See Abstract). Therefore, the claimed invention is anticipated by the cited reference.

19. Claims 213, 215-219, 26, 227, 231 are rejected under 35 U.S.C. 102(b) as being anticipated by Gowans et al. (WO 98/28004A1).

20. Gowance et al. teach a method for making a hepatitis virus like particle by co-expressing the HBsAg particle with 19 amino acid of COOH terminal sequence of the large protein from hepatitis D virus (L-HDAg), in which the L-HDAg as a target molecule for eliciting immune response, whereas HBsAg as the signal particle for forming virus like particle (see entire document). Therefore, the claimed invention is anticipated by the cited reference.

#### ***Claim Rejections - 35 USC § 103***

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

22. Claims 213-231 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kingsman et al. (WO 88/03563A1), Chackerian et al. (P.N.A.S, USA, 1999, Vol. 96, p. 2373-2378) and Tripet et al. (Protein Eng. 1996, Vol. 9, pp. 1029-1042).

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23. Claimed invention is directed to the method for making a virus like particle by using K-coil and E-coil sequences linked to the capsid protein of a virus like particle and a receptor target sequence respectively, wherein the capsid protein is preferred to be a retrovirus capsid protein gag and the target molecule is preferably the G-protein receptor. The K-coil/gag and E-coil/receptor will be non-covalently associated each other and expressed as a virus like particle. In this regard, the gag protein is a signal protein and the receptor is the target molecule. The second sequence of the signal molecule can be Ty element in the yeast etc.

24. Kingsman et al. disclose a method for making a retrovirus like particle by using a first amino acid and a second amino acid sequences, wherein the first amino acid sequence is derived from the retrotransposon (Ty) or an RNA retrovirus to assemble into a virus like particle (see entire document). Kingsman et al. does not teach to use the G-protein couple receptor as a target molecule.

25. Chackerian et al. teach a method for making a virus like by incorporating the CCR5, an G-protein coupled receptor with L1 coat protein of papillomavirus, which self-assemble into virus like particles. In this way, the CCR5 is a target molecule and L1 coat protein is a signal molecule for forming a virus like particle (see entire document). Chackerian et al. do not teach to use K-coil and E-coil sequences for making heterologous dimer protein during the virus particle formation.

26. Tripet et al. teach a method for using K-coil and E-coil sequence fused with two peptides or polypeptides to make a de-novo-designed coiled-coil heterodimerization of a protein structure. They explicitly disclose the K-coil and E-coil sequences and method for making the biotinylated K-coil, the method for making a heterodimer of a protein structure. They also teach several structural advantages made by the coiled -coil heterodimerization method, which include the purification, detection and eliminating any steric problem associated with improper folding of proteins attached to the tag, as well ensure the accessibility of enzymatic removal of the tag from peptides or proteins later in the method if desired.

27. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references and combine the teaching taught by Kingsman et al. Chackerian et al. and Tripet without unexpected results. Hence the claimed invention as a whole is *prima facie* obvious absence unexpected results.

***Conclusion***

No claims are allowed.

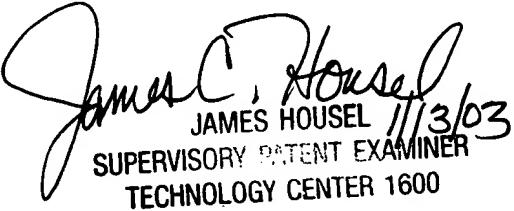
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li

January 2, 2003

  
JAMES C. HOUSEL 1/13/03  
SUPERVISORY PATENT EXAMINER  
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